



PATH MALARIA LEARNING SERIES

# The PATH Innovation Pipeline for Malaria

Transformative tools and approaches for defeating malaria



Making progress against malaria requires collaboration across borders, sectors, and disciplines. PATH engages and connects partners in the public, private, and nonprofit sectors—including country partners such as ministries of health and national malaria programs—to develop, evaluate, and scale tools and strategies to defeat malaria. Our partnership model translates bold ideas into products and strategies and leverages national capacity and enthusiasm in the fight against malaria.

#### THE PATH MALARIA LEARNING SERIES

The PATH Malaria Learning Series provides concise briefings on the latest evidence in malaria research and science. Each issue provides an overview of important developments in malaria control and elimination and synthesizes results from PATH-supported research.

#### ACKNOWLEDGMENTS

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#### IN THIS ISSUE

Innovation has been crucial to the remarkable progress made against malaria in the past 15 years. The development and introduction of a new generation of tools to fight malaria, such as artemisinin-based combination therapies, insecticide-treated bednets, and rapid diagnostic tests, have resulted in impressive reductions in the global malaria burden. Between 2001 and 2015, approximately 6.2 million lives have been saved, the vast majority of them among children in Africa under the age of five.<sup>1</sup> But malaria remains a devastating disease, imposing massive social and economic hardships on families and countries where the disease has yet to be eliminated. In 2015 alone, there were an estimated 212 million new cases of malaria worldwide, and more than 400,000 deaths.<sup>2</sup>

To sustain and accelerate progress against malaria, a new generation of tools and approaches is needed to address the gaps and limitations of existing technologies. These include the lack of a vaccine to protect against malaria and the lack of a highly sensitive diagnostic field test to rapidly detect low-density malaria infections, as well as growing resistance among malaria parasites and mosquitoes to commonly used drugs and insecticides. By filling gaps in the current toolkit and meeting emerging threats head on, innovative new tools and approaches will help to realize the enormous long-term benefits that will come from eliminating malaria in more countries and regions, and eventually eradicating it worldwide.

PATH is working in partnership with countries and organizations around the world to develop the next generation of tools and approaches to detect, prevent, and treat malaria. This issue of the PATH Malaria Learning Series explores PATH's innovation pipeline, which includes promising projects in vaccines, diagnostics, drugs (both developing new drugs and using existing drugs in new ways), and system and service innovations. These projects span the full development cycle, from upstream research and development to field implementation. Similarly, they extend across the technology spectrum, ranging from sophisticated vaccine development to scalable strategies that outfit volunteer health workers with malaria elimination tools. Defeating malaria will require a range of innovative strategies and solutions, and PATH's innovation pipeline provides many encouraging examples of the work that is now underway.

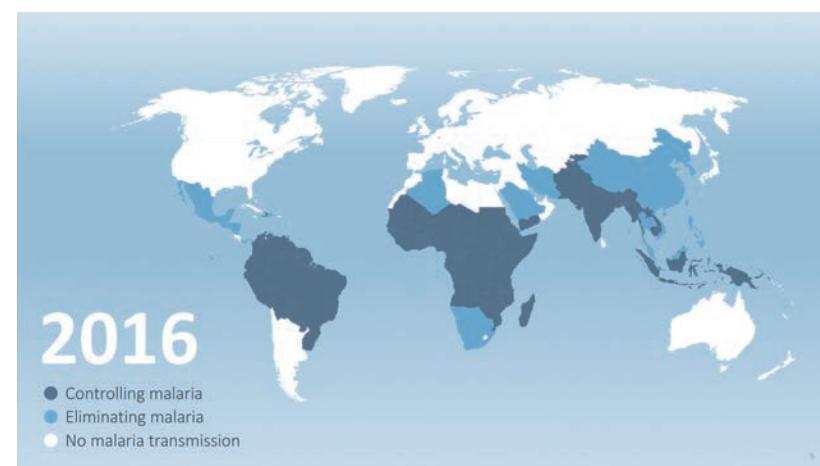
# The impact of innovation: 15 years of progress

Malaria is a mosquito-borne disease caused by the *Plasmodium* parasite. Malaria parasites are transmitted to humans by infected female *Anopheles* mosquitoes—the disease vector—that have acquired the parasite by biting infected humans. Because malaria parasites are transmitted in both directions between infected humans and mosquitoes, malaria transmission can be reduced either by stopping mosquitoes from infecting humans, or by stopping humans from infecting mosquitoes.

Remarkable progress has been made in the fight against malaria since 2000. The global malaria case incidence rate fell by an estimated 42 percent from 2000–2015, while the global mortality rate fell by an estimated 62 percent.<sup>2</sup> Approximately 6.2 million deaths were averted in this same period.<sup>3</sup> Advances against malaria have enabled the World Health Organization (WHO) to certify an increasing number of countries as malaria-free, with the number of countries with endemic malaria falling from 108 in 2000 to 91 at the beginning of 2016.<sup>2</sup> Many of the countries that still experience local malaria transmission have reduced malaria case numbers sufficiently to transition from the control phase to the elimination phase (Figure 1).

The development and introduction of a new generation of tools to fight malaria has been critical to these gains. Artemisinin-based combination therapies (ACTs) have proved highly effective for treating many types of malaria, while intermittent preventive treatment of malaria in pregnancy (IPTp) is helping to protect pregnant women and their developing fetuses from the adverse effects of malaria in pregnancy, including maternal anemia and low birthweight. Rapid diagnostic tests (RDTs) have transformed malaria care by drastically reducing the operational and financial hurdles to a quick, accurate, and affordable malaria diagnosis. Insecticide-treated bednets (ITNs) and new insecticide formulations for indoor residual spraying (IRS) are preventing malaria infections and reducing transmission. Sustained political commitment and funding increases since 2000 have greatly increased the supply of these life-saving interventions. Between 2000 and 2014, over 900 million ITNs were delivered to malaria endemic countries in sub-Saharan Africa, dramatically increasing access to this prevention tool.<sup>3</sup> Similarly, global RDT procurement rose from 88 million in 2010 to 270 million in 2013.<sup>2</sup>

Figure 1. Country progress against malaria from 1990–2016



Source: UCSF Global Health Group's Malaria Elimination Initiative. <http://www.shrinkingthemalariamap.org>.



# The continuing need for innovation

Despite the considerable progress achieved with the help of new tools, malaria remains a pervasive and lethal threat in many parts of Asia, Latin America, and particularly Africa. Pregnant women and their offspring are especially vulnerable. In Africa, malaria continues to be a leading cause of death in young children. Malaria is also an economic drain on communities and countries, contributing to loss of work and school time, and sometimes causing life-long disability. Moreover, drug and insecticide resistance—and the difficulty of sustaining political and financial commitments for combatting malaria—mean that the hard-won gains against malaria can erode.

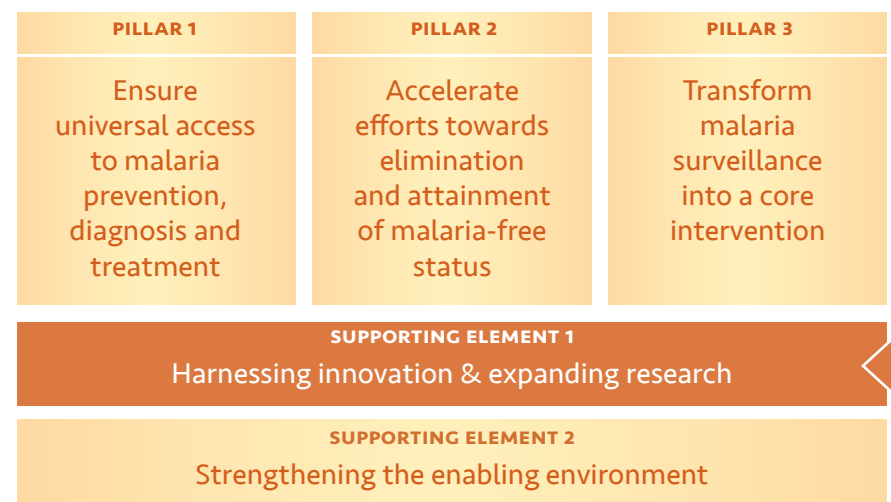
New tools and approaches can help meet these challenges by addressing some of the limitations and gaps of current tools. These needs include a more sensitive RDT to detect low-density malaria infections, which can be a source of ongoing transmission in the community. There are also pressing needs for a new generation of safe, effective, and affordable insecticides to stay ahead of insecticide resistance; further evaluation and deployment of vaccine candidates to prevent malaria infections; new strategies for using existing tools to accelerate malaria elimination; and innovative techniques for collecting and analyzing data. In recognition of these needs, the WHO Global Technical Strategy for Malaria states that harnessing innovation and expanding research is a necessary supporting element for meeting the strategy’s targets, which include reducing global malaria mortality rates and case incidence by at least 90 percent from 2015 levels by 2030 (Figure 2).

## PATH’S ROLE IN ACCELERATING INNOVATION

PATH-pioneered approaches have contributed to the progress made over the past 15 years. Now, PATH is accelerating progress with a broad portfolio of innovative tools and approaches to combat malaria. Among these projects, PATH is advancing development of new diagnostic tools for improving case management and detecting low levels of infection, managing and developing a number of vaccine candidates and approaches, working to evaluate new antimalarial drug strategies, strengthening the supply of affordable artemisinin therapies, and accelerating adoption of new IRS formulations.

PATH’s strategy for defeating malaria involves a multi-pronged and staged approach. This approach includes optimizing the delivery of current tools while developing new elimination strategies, creating next-generation tools

Figure 2. WHO Global Technical Strategy for Malaria 2016–2030



to meet unfilled needs and overcome emerging challenges, and building innovative partnerships and financing models to ensure sustainability and impact. PATH has a unique blend of technical expertise, relationships, and on-the-ground knowledge that it uses to identify promising new ideas, bring together collaborators, and advance projects in the malaria innovation pipeline. It also has a wide geographic footprint, with operations in more than seventy countries and a partnership network that extends to more than 2,000 partners worldwide. PATH leverages its relationships, local knowledge, and expertise to develop, adapt, and scale new tools and approaches for combating malaria.

PATH’s Center for Malaria Control and Elimination (CMCE) works across the malaria portfolio to align expertise and partnerships with the aim of accelerating development of strategies and tools for malaria elimination. This work is intended to empower national governments to pursue the goal of eliminating malaria transmission once and for all.

In the following sections, we present several major examples of PATH’s work in malaria diagnostics, vaccines, drugs, and system and service innovations, describing how new tools and approaches can help to overcome the gaps and limitations of current technologies.



Figure 3. Highlights from PATH's malaria portfolio



# DIAGNOSTICS

Malaria is preventable and curable, and early diagnosis and treatment of malaria decreases the risk of deaths and prevents the cycle of transmission, which is critical to achieving elimination. The WHO recommends that all cases of suspected malaria be confirmed using parasite-based diagnostic testing before administering treatment. Highly sensitive, cost-efficient, and field deployable tests are necessary to eliminate malaria and stop the disease's devastating impact on health and development. In collaboration with public and private sector partners, PATH is pioneering the use of diagnostics for malaria elimination. Our work is addressing the need for highly sensitive field tests to identify low-density malaria infections and to rapidly detect at the point of care a common heredity disorder that can complicate treatment for *P. vivax* malaria.



## NEW DIAGNOSTIC TOOLS FOR MALARIA ELIMINATION

In areas approaching elimination, a significant proportion of infections in a community may occur at levels of parasite burden that are undetectable by microscopy or current RDTs. These infections can represent a substantial source of malaria transmission, and yet go undetected. Highly sensitive rapid diagnostic tests may detect more of these infections for treatment and help to stop the cycle of transmission. PATH and our partners are advancing the rapid development, commercialization, and implementation of new, highly sensitive diagnostic tools for malaria elimination. In April 2017, Alere launched the Alere™ Malaria Ag P.f, an ultra-sensitive test for *P. falciparum* that was evaluated by PATH and partners. This new test has a tenfold improvement in detecting malaria markers, resulting in identifying a significantly larger proportion of people with malaria infections, and therefore creating an opportunity to halt the transmission cycle. Funding to PATH to support advancement of new highly sensitive tools for malaria has been provided by the Bill & Melinda Gates Foundation.



## G6PD DIAGNOSTICS

8-aminoquinolines such as primaquine are currently the only class of drugs known to achieve radical cure (the complete elimination of both the blood and liver stages of parasites from the body) of *P. vivax* malaria, a species commonly found in Asia and Latin America. *P. vivax* is especially challenging to eliminate because it can persist and cause relapses in infected individuals weeks or years after the original infection. Each subsequent relapse of disease results in incremental morbidity of the individual and a higher accumulated risk of mortality. As 8-aminoquinolines can be harmful to people with G6PD deficiency, a hereditary condition that is common in many malaria endemic areas, patients should be tested for the deficiency before these drugs are administered. PATH is advancing the availability of point-of-care tests for G6PD deficiency to support safe radical cure of *P. vivax* malaria.

GSK and the Medicines for Malaria Venture are collaborating in the development of tafenoquine, an investigational 8-aminoquinoline-based drug that targets *P. vivax*, including the form of the parasite that lies dormant in the liver. Through a collaboration with GSK, PATH is advancing the development of affordable quantitative point-of-care tests for G6PD deficiency that will support safe access to tafenoquine. Funding to PATH to support advancement of new G6PD diagnostic tools has been provided by the Bill & Melinda Gates Foundation and the United Kingdom Department for International Development.



# VACCINES

Historically, vaccines have offered one of the most effective means of preventing infectious diseases and saving lives. In light of international goals for controlling, eliminating, and eventually eradicating malaria, a vaccine is seen as adding an important and complementary tool to the broader toolkit of malaria interventions. PATH's pipeline of vaccine candidates and approaches, under development with partners from across the globe, is one of the most robust in the world. It includes candidates that would prevent infection and those that attempt to block transmission of the malaria parasite from humans to mosquitoes and back again.



## THE RTS,S VACCINE

The RTS,S vaccine candidate (known as Mosquirix™) being developed in partnership by PATH and GSK is the vaccine most advanced in development globally. It is intended to complement existing measures to fight malaria such as ITNs and IRS. As with all vaccines, RTS,S aims to trigger the body's own immune system to defend against disease—in this case, malaria caused by *P. falciparum*, the most deadly species of the malaria parasite. Specifically, RTS,S is designed to prevent the malaria parasite from infecting, maturing, and multiplying in the liver, after which the parasite would normally re-enter the bloodstream and infect red blood cells, leading to disease symptoms. Clinical study results indicate that RTS,S has the potential to help protect infants and young children living in malaria endemic regions in sub-Saharan Africa.

Results of the pivotal Phase 3 efficacy and safety trial showed that RTS,S reduced the number of malaria cases by half, over the first year of follow-up, in children 5 to 17 months old who received three doses of the vaccine. Efficacy waned over time, but was prolonged by the fourth dose given 18 months after dose 3, resulting in the prevention of 4 malaria cases out of 10 over four years of follow-up.

## RTS,S PILOT IMPLEMENTATION

After decades of research and testing, and dozens of clinical trials involving more than 19,000 children, RTS,S received a positive Scientific Opinion from European regulators in July 2015. In January 2016, it was recommended by WHO for pilot implementation in 3–5 settings across sub-Saharan Africa to further evaluate safety, impact, and operational feasibility. With financial support from UNITAID, GAVI, and the Global Fund, WHO and partners—including PATH and GSK—are moving forward with pilot implementation of RTS,S. The vaccine will be available in selected areas in Ghana, Kenya, and Malawi, through a pilot program, coordinated by WHO, beginning in 2018. The RTS,S Project at PATH will provide technical assistance to WHO in a number of areas, including economic assessments, pharmacovigilance, and behavior change research.

## RTS,S DELAYED FRACTIONAL DOSE

Recently, promising evidence became available that indicates that a reduced content of the third vaccine dose administered according to a different dosing regimen may actually be more effective. The results of two clinical studies that provided delayed fractional dosing of RTS,S to adult volunteers have been encouraging, and PATH is partnering with GSK and the Walter Reed Army Institute of Research (WRAIR) to conduct a controlled human malaria infection (CHMI) study to further test and refine the fractional dose approach. In parallel, planning is underway for field studies in two African countries to see if the results can be replicated in adults and young children in Africa. These studies should begin in 2017. If results can be replicated in the field, this modified regimen of RTS,S could more effectively protect children from the disease, and, if implemented more broadly across affected communities, help drive down transmission of the malaria parasite to accelerate elimination efforts.

## MONOCLONAL ANTIBODIES

In recent years, PATH has led efforts to identify and characterize monoclonal antibodies (mAbs) that block parasites from infecting humans and from transmitting to mosquitoes. While these antibodies are helping to answer important technical questions, including to inform vaccine design, there is increasing interest in their potential to serve as supplemental interventions to accelerate elimination. Declining manufacturing costs, combined with powerful new technologies that can improve potency and pharmacokinetic properties, are propelling mAbs toward consideration for use in developing countries. Over the next two to three years, PATH will advance two mAbs, one each that blocks infection and transmission, to initial efficacy testing in human volunteers. The outcomes of these studies will help inform the potential utility of mAbs as interventions.



# DRUGS

Antimalarial drugs are a critical tool for controlling and eliminating malaria. WHO recommends ACTs as the first-line treatment for *P. falciparum*, the most deadly form of malaria. ACTs are particularly effective because they combine fast-acting compounds that quickly kill the majority of parasites with a slower acting drug that clears the remaining parasites. Maintaining an adequate supply of effective antimalarial drugs, while finding more efficient and targeted ways to deliver them where they are needed most, will be crucial elements in the fight against malaria.



## SEMISYNTHETIC ARTEMISININ

The global supply of artemisinin, a key ingredient in the manufacture of ACTs, can be volatile because of market imbalances between supply and demand. This has led to price fluctuations for this plant-derived compound that complicate supply planning and increase the risk of a global shortage. To strengthen the artemisinin market and help ensure an uninterrupted flow of ACTs to malaria endemic regions, PATH set out to create a supplementary source of artemisinin. Using synthetic biology technology, PATH and partners in the research, biotech, and pharmaceutical sectors successfully developed and introduced semisynthetic artemisinin as a supplementary source of the key ingredient in ACTs. Semisynthetic artemisinin offers additional capacity to help meet market demand as needed, and is WHO-prequalified and commercially available to qualified manufacturers.



## POPULATION-WIDE DRUG-BASED STRATEGIES

Population-wide drug-based strategies, which include mass drug administration (MDA), are potentially powerful accelerators for malaria elimination when used in a time-limited manner and in combination with other interventions. MDA is a campaign-style intervention in which health personnel go door-to-door to reach as many people as possible in a designated population (e.g., a village, set of villages, or entire district) in a short time period. Because an entire population is targeted for treatment, MDA can clear malaria infections that might not be picked up by diagnostic tools with limited sensitivity.

If drugs with a long duration of effect are used, MDA can also provide a prophylactic effect to the whole population. MDA aims to reduce malaria transmission to low enough levels that the program can move to a strategy of timely surveillance coupled with case investigation to identify and treat remaining cases without becoming overwhelmed by the number of individuals seeking care. PATH-supported operational research in Zambia suggests that MDA with dihydroartemisinin-piperazine (DHAP), an antimalarial drug with a sustained prophylactic effect, may be a useful time-limited strategy to rapidly reduce the parasite burden in a population.





# SYSTEM AND SERVICE INNOVATIONS

Enhancing systems and services that support the development, introduction, scale-up, delivery, and evaluation of new malaria tools is essential for defeating malaria. System and service innovations can help increase access to lifesaving malaria commodities, strengthen diagnosis and treatment, and improve data collection and management. Ultimately, the aim is ensure that health care providers and decision-makers get the most out of available resources, target them where they can have the most impact, and track progress toward goals.



## DATA ANALYTICS AND VISUALIZATION

Visualize No Malaria is a partnership between the Zambia Ministry of Health, PATH, Tableau, and others that uses near real-time data, analytics, and data visualization to facilitate data-informed decision-making for malaria elimination. Visualize No Malaria is launching in Zambia, a country that has set an ambitious goal of eliminating malaria nationwide by 2021. The partnership is providing software and training to district-level and frontline health workers so they can better track, treat, and ultimately prevent malaria cases and make local resourcing decisions based on the best available data. Using interactive dashboards for fast, customizable data visualization, decision-makers will have timely information on outbreaks, transmission patterns, and progress toward strategic plan objectives. The Visualize No Malaria initiative in Zambia serves as a potential model for future public-private partnerships in other countries working to eliminate malaria.



## NEW CLASSES OF INSECTICIDES FOR IRS

Vector control—reducing or interrupting malaria transmission through measures to limit the mosquito population and stop mosquitoes from biting humans—is a foundation of malaria prevention. However, growing mosquito resistance to the insecticides currently used in ITNs and IRS is threatening to diminish the efficacy of these tools. Next Generation IRS (NgenIRS) is a partnership led by the Innovative Vector Control Consortium (IVCC) to expand access to new antimalarial insecticides in Africa that are highly effective in the setting of current resistance levels. Funded by UNITAID, NgenIRS will work to bring down the price of new insecticides through UNITAID co-payment mechanisms, improved procurement forecasting, and manufacturer competition. NgenIRS aims to help as many as fifty million people at risk for malaria receive protection from new IRS formulations over the next four years. NgenIRS partners include the US President's Malaria Initiative (PMI), Abt Associates, the Global Fund, and PATH's Results Management, Measurement, and Learning (RMML) department. PATH's role in NgenIRS is to work with national malaria control programs to increase the availability of evidence on the cost effectiveness of new insecticides in countries with high malaria burdens.



## Conclusion

PATH's vision is of a world free from malaria: one in which the global community and partner countries have the tools, financial capacity, and political will to control, eliminate, and ultimately eradicate malaria. PATH's partnerships with countries, the private sector, and global stakeholders to innovate, develop, and apply technologies and program strategies to reduce malaria's health and economic burden have already made a difference. Going forward, PATH will leverage its scientific expertise, global partnerships, and local experience to continue development, introduction, and evaluation of the projects in its malaria portfolio. From new vaccine candidates, vector control interventions, and diagnostic tools, to community-level strategies to detect and treat hard-to-find malaria cases, PATH's innovation pipeline of tools and strategies will help bring us even closer to a world without malaria.



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PATH is a leader in the battle to control and eliminate malaria nationally, regionally, and ultimately to eradicate it worldwide. PATH is partnering with national programmes to optimize the delivery of current solutions and approaches, while developing new strategies to eliminate malaria in local and regional settings. With an unparalleled portfolio of malaria projects, PATH is developing the next generation of tools to accelerate efforts to detect, prevent, and treat malaria and to control mosquitoes.

**Diagnostics.** In collaboration with public and private sector partners, PATH is pioneering the use of diagnostics for malaria elimination. We are improving access to available tests while advancing the development of new ones that support improved case management.

**Vaccines.** PATH's pipeline of vaccine candidates and approaches, under development with partners from across the globe, is one of the most robust in the world. It includes candidates that would prevent infection and those that attempt to block transmission of the malaria parasite from humans to mosquitoes and back again.

**Drugs.** PATH is working to improve malaria treatment so that no one who contracts the disease dies from it. We are ensuring a stable supply of malaria drugs and strengthening the existing supply. We are also strengthening health systems and improving the quality of malaria case management in Africa and the Mekong Region.

**System and Service Innovations.** To develop the science behind how to eliminate malaria in Africa, we are piloting new strategies with the goal of developing a package of approaches that are adoptable and adaptable across the region. These include strategies to stop the transmission of the malaria parasite from humans to mosquitoes and back again through community-wide treatment. We are collaborating closely with endemic countries to create malaria-free zones, the first step on the path to elimination.

**Better Data for Decision-Making and Improved Surveillance.** PATH is working with partners to use data in new and better ways to track emerging transmission patterns, optimize the way resources are deployed, and eventually track down the last malaria parasite.



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